LESIONS OF TESTES OBSERVED IN CERTAIN PATIENTS WITH WIDESPREAD CHORIOCARCINOMA AND RELATED TUMORS

The Significance and Genesis of Hematoxylin-Staining Bodies in the Human Testis

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The significance of testicular scars as sites of healed primary gonadal tumors in patients with extragenital choriocarcinoma has long been known,[1] as has also the association of a small adult teratoma of testis with widespread metastasis.[2] A detailed study of a number of such cases from the files of the Testicular Tumor Registry of the Armed Forces Institute of Pathology yielded other interesting results which we believe merit publication.

Material

The 17 cases utilized in this investigation were those in which the patients had died with widespread tumors consisting of choriocarcinoma in 8 instances, embryonal carcinoma in 5, mixtures of choriocarcinoma and embryonal carcinoma in 3, and teratocarcinoma and embryonal carcinoma together in 1 case. The patients were all young men. Gynecomastia was reported in 11 patients, 7 of whom had choriocarcinoma. In all 17 the testicular lesion consisted only of a fibrous scar in which viable neoplastic tissue was either absent or of minute size (not exceeding 5 mm. in diameter). Testes containing a hemorrhagic focus in which little recognizable neoplasm was identifiable were excluded, since it is well known that these may represent instances of choriocarcinoma with scanty residual viable primary tumor tissue.[3] Also excluded were examples of minute teratoma of testis in patients who were not examined at necropsy.

As controls, the testes were examined from 60 patients with interstitial cell tumors, 20 patients with Sertoli cell tumors, 65 young patients dying from automobile and other accidents, 80 patients dying of malignant neoplastic disease of all types, and 25 patients with primary mediastinal teratoid tumors.

Pathologic Observations

The incidence and types of testicular lesions are shown in Table I. The most frequent lesion consisted of a more or less well-defined fibrous

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TABLE I

INCIDENCE AND TYPE OF TESTICULAR LESIONS

AFIP acc. no.	Shape of scar	Location	Hematoxylin deposits	Siderophages	Teratomatous tissues	Atypical cells in surrounding tubules	Microscopic focus of seminoma	Histology of metastases	Gynecomastia
106546	Irregular	Not known	—	—	Epidermoid cyst, 3 mm. diam.	—	—	Embryonal carcinoma and choriocarcinoma	+
132104	Irregular	Not known	+	+	—	+	+	Choriocarcinoma	+
142203	Rounded	Not known	+	++	Ruptured epidermoid cyst (with a few cholesterol clefts).	+	—	Embryonal carcinoma and choriocarcinoma	+
150705	Irregular	Near rete	+	—	Three microscopic cysts, 2 lined by columnar epithelium, 1 without its lining.	+	+	Choriocarcinoma	+
161897	Irregularly linear	Near rete	+	+	—	—	—	Embryonal carcinoma and choriocarcinoma	—
168079	Irregularly rounded	Upper pole, testis	—	++	—	+	—	Embryonal carcinoma	—
281811	Stellate	Near rete	—	+	—	+	—	Teratocarcinoma and embryonal carcinoma	—
293443	Stellate	Near rete	++	—	—	+	—	Embryonal carcinoma	—
323501	Irregularly rounded	On posterior surface of testis beneath tunica (relation to rete not determined).	++	—	—	+	—	Choriocarcinoma	—

335808	Elongated, bandlike	Near rete	+	−	−	+	−	Embryonal carcinoma	+
533124	Irregularly rounded	Near rete	++	−	−	−	−	Choriocarcinoma	+
589674	Irregular	Near rete	++	−	Microscopic squamous foci; mucous cyst; neuroglial tissue. Degenerating carcinomatous cells.	+	+	Choriocarcinoma	+
650216	Irregular	Not known	+	−	−	+	−	Embryonal carcinoma	−
658096	Irregularly rounded	Near rete	++	−	Eight or 9 microcysts (together measuring 3-4 mm. diam.). Lined by attenuated mucous cells or have desquamated lining. One mucous cyst surrounded by layer of smooth muscle.	+	−	Choriocarcinoma	+
747941	Elongated	Not known	−	+	Two epidermoid cysts, together measuring 3-4 mm. in length.	+	−	Choriocarcinoma	+
819008	Irregular	4 mm. from rete	++	−	One epidermoid cyst. A few malignant cells mixed with hematoxylin material.	+	+	Embryonal carcinoma	+
927471	Irregular	Near rete	+	+	Cluster of cysts, together measuring 3-4 mm. diam.; at least one lined by mucous cells with a few Kultschitzky cells.	−	−	Choriocarcinoma	+

scar (Fig. 1), often containing the ghostlike remains of hyalinized seminiferous tubules. The scar was usually irregular in shape, sometimes linear, wedge-shaped, or irregularly rounded. It consisted of relatively acellular collagenous tissue, usually dense but sometimes loose, and contained an occasional mast and plasma cell. In 10 of the 17 cases, the scar was situated in the neighborhood of the rete testis (Fig. 1), and in only 1 was it known to have been situated at the pole of the testis. Siderophages were present in 7 of the scars, in moderate numbers in 5 and in large numbers in 2 (Fig. 2).

In 13 of the cases, in addition to the scars, peculiar hematoxylin-staining deposits were observed (Figs. 1 and 3). These deposits appeared as rounded or ovoid foci sharply separated from one another by a basement membrane and intervening scar tissue. They were compactly arranged in a small portion of the scar or scattered uniformly through it. Their size and general configuration, and in particular the hyaline, thickened basement membrane surrounding each one, suggested strongly that the deposit was located within dilated seminiferous tubules (Fig. 3) and not in vascular channels. The hematoxylin-staining material was not accompanied by red cells, fibrin thrombi, or organizing thrombi; there was no smooth muscle in the surrounding wall. Hematoxylin-staining foci were present only in sites where seminiferous tubules were found and not in vascular channels. For further confirmation, one case (AFIP Acc. No. 589674) was examined in serial sections, and the hematoxylin deposits, Sertoli cells, and a corpus amylaceum were all observed within the same basement membrane. The deposits had an amorphous, granular, unorganized structure (Fig. 3). Sometimes they appeared as larger irregular fragments in an amorphous matrix.

In two instances, malignant neoplastic cells were recognizable within tubules, associated with the hematoxylin-staining substance (Fig. 4). These cells did not have the sharp outlines of the neoplastic cells in intratubular seminoma, and they had vesicular nuclear features suggesting undifferentiated tissue of the type seen in embryonal carcinoma.

The tissue around these aggregates was sometimes torn in the process of sectioning, suggesting calcification of the deposits. Von Kossa staining showed that phosphate was, in fact, often present, and staining with alizarin red established the presence of calcium. The hematoxylin staining was not, however, due to lime salts since calcium *per se* is not hematoxylinophilic.[4] The deposit often stained in positive manner and occasionally deeply with Mayer's mucicarmine. More significantly, Feulgen-positive[5] material was found frequently in these foci, indicating that mucoid substances and deoxyribonucleic acid (DNA) were responsible for most of the hematoxylin staining. Staining of paraffin

sections with Sudan black B [5] showed the presence of formol-fixed lipid in the deposits; these also gave a strongly positive reaction with Baker's acid hematein method.[5] The periodic acid-Schiff reaction was only weakly and variably positive. The Danielli coupled tetrazonium method [5] yielded a positive result, with a bright orange color in the tubular deposits, indicating the presence of tyrosine, tryptophan, or histidine. This occurred in spite of formalin fixation, which is likely to reduce the intensity of the reaction because of blocking in aromatic hydroxyl groups. Millon's reaction [5] demonstrated the presence of tyrosine. The hematoxylin deposits were composed, therefore, of an amorphous, complex mixture of phospholipid, protein, and scanty 1–2 glycol groups in combination with DNA. Some specimens, but not all, contained, in addition, mucicarminophilic material and calcium phosphate; calcium was not an essential part of the complex, however.

In addition to the scars and hematoxylin-staining bodies, certain neighboring viable tissues were seen. Teratomatous elements were present in 8 cases in close proximity to the scars. Although initially missed or interpreted as congenital rests, these consisted of epidermal cysts (Figs. 1 and 5) containing keratin in 4, mucous cysts in 2 (Fig. 6), and both types of cysts in another case; one contained 2 minute cysts lined by columnar non-mucus-secreting epithelium. In one of the lesions a mucous cyst was surrounded by a thick layer of smooth muscle. In the scar containing both mucous and epidermoid cysts, there was also some neuroglial tissue. A few typical enterochromaffin cells were present in the epithelial lining of one mucous cyst (Fig. 7).

In two cases (Acc. Nos. 168079 and 281811) the scars did not contain recognizable teratomatous tissue or hematoxylin-staining deposits. One was an irregularly rounded scar, 1.5 by 0.6 cm., near the upper pole of the testis, containing large numbers of siderophages (Fig. 2); the other was an irregularly stellate scar in the rete testis, containing few siderophages.

In 4 instances a microscopic focus of seminoma was encountered in the tissue surrounding the scarred area, in each case occupying no more than a fraction of a high-power field (Fig. 8). A far more prominent finding than these minute seminomatous foci was an alteration in the seminiferous tubules adjacent to or a short distance from the scarred area. These sometimes involved a considerable zone of tissue, and were evident in many blocks (Fig. 9). Where this change was present, spermatogenesis had ceased and the tubules usually showed hyalinization and contained only these atypical cells. Frequently there was an associated inner layer of Sertoli cells (Fig. 10) and at other times these filled the lumen.

The remaining portion of the testis usually showed atrophy of semini-

ferous tubules, hyalinization of basement membrane, and hyperplasia of interstitial cells.

Illustrative Cases

Two examples have been selected to illustrate the problems that may be encountered with this type of lesion.

Case 1 (AFIP Acc. No. 161897)

The patient was a 21-year-old white male. The first symptom was blood-stained sputum. Slight shortness of breath with chest pain developed within 1 month. Two months later he complained of pain in the right lumbar region. Shortness of breath became more marked, and he developed pain in the left lower chest. His appetite was poor, and he lost weight. Examination on admission revealed an acutely ill patient. The right apex posteriorly and the entire left lung field were dull to percussion. A large, hard, tender mass was palpable in the epigastrium. The clinical course was progressively downhill. A month later he became mentally confused and had severe coughing bouts, with expectoration of blood. He became comatose and died just over 4 months after his initial symptoms. Neither the correct diagnosis nor the possibility of a primary testicular neoplasm were suspected.

Necropsy revealed tumor deposits in the lungs, liver, ileum, and brain. The largest, weighing 220 gm. and measuring 9 by 6 by 5.5 cm., was situated in the retroperitoneal tissues. The mass lay to the right and below the junction of the second and third portions of the duodenum, and anterior to the right kidney and psoas muscle. It partially surrounded the inferior vena cava and aorta. The anterior wall of the vena cava was invaded by the neoplasm, which projected slightly into its lumen and was covered by a small amount of thrombus. On section, the mass had a variegated appearance, dark and light red with pale yellowish areas. The testes appeared normal in size and color and showed no macroscopic abnormality. Microscopic examination of the retroperitoneal mass and other tumor deposits showed embryonal carcinoma and choriocarcinoma. Sections of the testes were originally regarded as normal, and the possibility of a primary retroperitoneal teratocarcinoma with choriocarcinomatous differentiation was entertained. Re-examination of the testicular sections, however, showed a small linear scar containing intratubular hematoxylin-staining deposits. This was considered to be a healed primary testicular tumor.

Case 2 (AFIP Acc. No. 589674)

A 26-year-old white male had been in good health until 4 weeks before admission, when he complained of malaise, severe cramps, and some blood and mucus in the stools. He then noted left subcostal pain and persistent back pain. In the 4 weeks he lost 20 pounds. Severe anorexia and vomiting developed, and at the time of admission, severe pain over the sacrum and in the left flank were the main complaints. Inquiry elicited the information that about 4 or 5 years previously he had had some intermittent swelling and tenderness of both breasts.

Examination showed a thin man in moderate discomfort. There was tenderness over the epigastrium and left upper abdominal quadrant, and a nodular, hard mass, about 10 cm. in diameter, was palpable in the left hypochondrium. The testes appeared normal. There was bilateral gynecomastia, more pronounced on the right, with indurated breast tissue, 5 cm. in diameter, beneath the enlarged right nipple. Estimation of follicle-stimulating hormone excretion revealed 80 mouse units per 24 hours (normal for age, 8 to 20 units). Chorionic gonadotrophin level was 549,000 mouse units per 24 hours (normal, 0). Urinary estrogen assay was 34 gamma per 24 hours (normal for age, 2.5 to 10 gamma), and the 17-ketosteroid level was 17.1 mg. per 24 hours (normal, 10 to 20 mg.). Radiologic examination showed the stomach to be displaced to the right and anteriorly by a retroperitoneal mass in the region of the left kidney. Roentgenograms of the skull and lumbar spine revealed no lesions. A chest film showed many small, rounded deposits within the lung fields. Excretory urograms revealed a nonfunctioning left kidney.

A month after admission to the hospital the patient was treated with stilbestrol, 50 mg. 4 times daily. In an effort to determine the site of the primary lesion, 2 testicular biopsy examinations were made, but with negative results. The patient remained anemic, with a hemoglobin level below 8 gm. per 100 ml., despite blood transfusions. He became very dyspneic. Four hundred cc. of dark red blood was removed from the left pleural space. He remained in an oxygen tent until death, about 6 weeks after admission and 10 weeks after the onset of symptoms.

At necropsy, choriocarcinoma was found in the liver, lung, brain, kidney, spleen, vertebral bone marrow, and retroperitoneal soft tissue, including the left psoas muscle. There was bilateral gynecomastia. The right testis contained several reddish-yellow areas of discoloration and the left testis, many reddish foci. There was no tumor recognizable macroscopically, however, in spite of careful examination of many parallel slabs. Both testes contained zones of infarction, probably the result of surgical trauma. Leydig cell hyperplasia was more prominent in the left testis. In the region of the left rete testis a collagenous scar containing several minute squamous nests and cysts, one lined by mucous cells, was found along with some neuroglial tissue. There were hematoxylin-staining deposits and degenerating malignant neoplastic cells within a few tubules. The left testis is considered to be the primary site.

Discussion

Small focal scars secondary to trauma or orchitis are not unusual in the testes of adults. Circumscribed scars containing hemosiderin or calcification of the type reported by us, however, have not been observed except in patients with metastatic choriocarcinoma, embryonal carcinoma, or teratocarcinoma. Prym[1] is credited with the first report of a case of this type in which a testicular scar containing brown pigment was associated with choriocarcinomatous metastases. Heaney's case[6] was interpreted by him as an example of extragenital choriocarcinoma, but Symeonidis[7] and Roth[8] both regarded the hemorrhagic testicular scar as a retrogressed primary tumor. Michel[9] reported a further in-

stance, and Eck's first case[10] of testicular tumor with a pea-sized scar in the testis is probably similar. In Roth's series of testicular tumors,[8] a scar near the rete was associated with choriocarcinomatous metastases and gynecomastia in case 9. Roth mentioned intratubular calcification in his case. Friedman[11] referred to several scars of this type, with or without calcification. Rather, Gardiner and Frerichs[12] reported 6 new cases which, with the 18 they had accumulated from the literature, showed either a scar, foci of seminoma, or cysts and tubular structures in the zone of testicular fibrosis. Maluf, Loeffler and Erickson[13] also reported focal areas of fibrosis and patches of calcification associated with an adult testicular teratoma in a patient with widespread choriocarcinoma. More recently Maring, Knopp and Langecker[14] also considered a scar in the testis as primary in a patient who died of widespread choriocarcinoma.

Calcification is not unusual in the testis. The most common forms of calcified bodies are mucospherules or concretions found in atrophic seminiferous tubules (Fig. 11). These are smoothly rounded bodies with a concentrically laminated structure; they occupy the tubular lumens and are occasionally surrounded by a single residual layer of Sertoli-like cells. These psammoma-like bodies are seen frequently in cryptorchid testes and, in these, they are associated with the multiple tubular "adenomas" or foci of Sertoli cell hyperplasia common in undescended testes (Fig. 12). The concretions are also observed in atrophic seminiferous tubules surrounding any type of testicular neoplasm, and in these circumstances may become "caught up" in the neoplastic process. These bodies are probably related to abnormal activity of Sertoli cells. They are somewhat analogous to corpora amylacea in the prostate or lung. The mucospherules may be either eosinophilic or hematoxylinophilic. They stain feebly with mucicarmine; sometimes a small central core appears carminophilic while the periphery remains unstained. On the other hand, they give an intensely positive PAS reaction. Even when the calcified bodies are fragmented in the process of sectioning, their laminated structure is usually still discernible.

Less frequently, calcific deposits may be seen in healed inflammatory lesions and in certain primary tumors of the testis in the form of granular calcium salts.

In contrast to these, the amorphous and granular hematoxylin-staining bodies described in this investigation and not seen in any of the control testes are quite distinct from the corpora amylacea and the calcifications of inflammatory origin. By histochemical technique we have demonstrated that these hematoxylin bodies are composed of a complex mixture of phospholipid, protein and scanty 1-2 glycol groups, DNA and

calcium phosphate. Calcium, while present, is not an essential component. It may be safely assumed, therefore, that the hematoxylin bodies represent necrosis of nuclear chromatin. That such a possibility does exist is suggested by Friedman's observation [11] that choriocarcinoma, by virtue of its tendency to blood vessel invasion, may cause infarction of considerable extent. The intratubular neoplastic tissue accompanying the hematoxylin-staining material, seen in 2 of our cases, represents an undifferentiated form of malignant tumor. It may well be that the high metabolic turnover of such neoplastic cells, perhaps, associated with a poor blood supply, leads to massive necrosis of the intratubular tumor.

The significance of the hematoxylin-staining bodies was further investigated. They were not infrequently observed in grossly recognizable testicular teratoid tumors (Figs. 13 and 14) not included in this study of 17 cases. In a number of these the transformation of recognizable intratubular malignant elements to granular debris could be traced. It is significant that in these cases the neoplastic cells were undifferentiated and did not resemble either germ or seminoma cells.

In 8 of our patients minute teratomatous structures were observed. These were similar to those reported by Stärk,[2] Craver and Stewart,[15] Symeonidis,[7,16] Rottino and DeBellis,[17] and Riopelle.[18] In 4 patients microscopic seminomas were associated with hematoxylin-staining bodies and teratomatous structures.

Another frequent finding was a peculiar alteration observed in 13 cases. This was characterized by large hyperchromatic cells with a small amount of vacuolated cytoplasm. These cells occurred inside seminiferous tubules and resembled germ cells. They were identical to the cells described by Dixon and Moore[3] in the rete testis of some of their examples of invasive seminoma. Similar cells were not observed in any of our control specimens; we have seen them most frequently in the seminiferous tubules of patients with seminoma and occasionally they have been associated with other germ cell tumors of the testis. Their significance and possible relationship to the genesis of teratoid tumors of testes is under investigation.

Thus, in a group of 17 patients, 11 with gynecomastia, widespread metastases of either choriocarcinoma or embryonal carcinoma have been observed at necropsy. In these cases certain lesions have been observed in the testis, consisting of a circumscribed scar and intratubular hematoxylin-staining material with a high DNA content. These have sometimes been accompanied by small teratomatous structures and in a few cases by microscopic foci of seminoma. The occurrence of these testicular structures in patients with generalized metastatic growths would

appear to provide satisfactory circumstantial support for the theory of retrogression in primary testicular tumors.

The appearance of hematoxylin-staining bodies in well defined teratoid testicular tumors leaves no doubt that they represent cellular debris resulting from ischemic necrosis of neoplastic tissue. These deposits are located almost exclusively within tubular structures. Although dilated, the tubules are most probably either seminiferous tubules or ducts. It is possible that necrotic debris in this location is removed with difficulty and forms an inspissated matrix in which calcium salts may be deposited.

Although the 17 cases investigated were all examined at necropsy, and the testicular lesions observed were not found in 250 control testes, it cannot be assumed that such lesions always lead to generalized dissemination of tumor. It must be borne in mind that these lesions were frequently detected only after careful search and special study of the testes in patients who had metastatic tumors of apparent germ cell origin. It is possible that a number of these testicular lesions, in fact, may remain quiescent and never give rise to metastases. Similarly, it may be that in patients without gynecomastia or metastatic choriocarcinoma but with generalized metastases of less distinctive germ cell tumors of other types, the testes are either superficially examined or not examined at all. Thus, a minute primary tumor, whether viable or having undergone retrogression, may be missed. The high coincidence of choriocarcinoma and gynecomastia in this group of cases may, therefore, be genuine or reflect case selection.

Our observations have a bearing on the question of the existence of primary extragonadal choriocarcinoma in the male. Cases have been reported in the retroperitoneum and the peritoneal cavity, in the mediastinum, and in the pineal, as well as in various organs.[19–22] We believe that skepticism is justified in most cases of this type. This applies particularly to the cases [6,23,24] in which incidental lesions found in the testes should probably be re-interpreted as examples of neoplastic retrogression. We consider it essential that the testes from patients of this type be carefully and serially examined. Only if no lesions are found may the case be accepted as an example of extragonadal choriocarcinoma.

So far there have only been about 30 cases reported in which careful examination of the testes showed no probability of primary neoplasm in this location.[19,20,22,25–27] Stowell, Sachs, and Russell,[22] however, have questioned (a) the evidence indicating spontaneous healing of primary chorionepithelioma while the metastases continue to grow, and (b) the significance of scars in the testes. Lynch and Blewett[21] have offered the intriguing possibility that "testicular scars" (reported as the alleged site of burned-out primary tumors in patients with widespread chorio-

carcinomas) "might themselves be the results of extragenital growths" and that "the intense hormonal stimulation may cause totipotent gonadal cells to develop into small teratomata." While absolute proof may be lacking, we believe that the testicular scars and the other lesions of the type described by us constitute the primary foci from which widespread dissemination of choriocarcinoma and related tumors may occur. Similar lesions were not observed in any other condition or in the contralateral unaffected testes of patients with metastatic choriocarcinoma or in other patients with primary extragonadal choriocarcinoma.

The intratubular location of the hematoxylin-staining bodies as well as the appearance of malignant neoplastic cells in the tubules offers evidence in support of an intratubular origin of teratoid testicular tumors, a concept already accepted for seminoma.[3,28] A secondary extension into the tubules in 13 of 17 cases by such minute foci of neoplastic tissue would seem highly unlikely. In seminoma it is often possible to trace the tubular origin of the lesion even when the tumor has attained a considerable size. In embryonal carcinoma and other teratoid testicular tumors, this feature is rather rare unless the tumor is seen very early or is undergoing regression. The long-standing controversy over the origin of testicular teratoid tumors mainly centers about the concept of escape by embryonic median or paramedian tissue from the influence of a primary organizer [29] versus the germ cell theory of origin. The presence of genuine choriocarcinoma in teratoid testicular tumors favors the latter hypothesis, and the possibility of origin of these tumors by fusion of haploid cells has received great support from recent work on the nuclear sexing of the neoplastic tissue.[30] The tubular localization of testicular teratoid neoplasms which have undergone partial regression suggests a probable tubular origin for embryonal carcinoma and related tumors, an observation which further supports the concept of germ cell origin for these neoplasms.

Summary

In 17 patients with widespread choriocarcinoma and related neoplasms, frequently with associated gynecomastia, certain lesions have been observed in the testes. In all instances a distinct and well defined fibrous scar was found. In addition, in 13, peculiar amorphous hematoxylin-staining deposits were observed in dilated seminiferous tubules. By histochemical methods, these deposits were shown to consist of phospholipid, protein debris, and DNA, and in some cases, mucoid substances and calcium phosphate. Believed to originate from the necrosis of undifferentiated neoplastic tissue of germ cell origin, the presence of these hematoxylin deposits lends support to earlier reports of burned-out

primary testicular tumors. In 8 cases there were remnants of mature teratoma, and in 4 there were microscopic foci of seminoma in relation to the scars.

The observations are interpreted to indicate regression of primary testicular tumors. Biologic factors responsible for regression in a primary neoplasm remain to be established. Certain alterations were also observed in the germ cells of the testis adjacent to the scar; the significance of these could not be determined.

References

1. Prym, P. Spontanheilung eines bösartigen, wahrscheinlich chorionepitheliomatösen Gewächses im Hoden. *Virchows Arch. path. Anat.*, 1927, **265**, 239–258.
2. Stärk, A. Malignes Chorionepitheliom bei einem 28jährigen Soldaten mit kleinem Embryom des Hodens. *Frankfurt. Ztschr. Path.*, 1918, **21**, 142–162.
3. Dixon, F. J., and Moore, R. A. Tumors of the Male Sex Organs. Section VIII, Fascicle 32, Atlas of Tumor Pathology. Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Armed Forces Institute of Pathology, Washington, D.C., 1952, p. 59.
4. Azzopardi, J. G. Oat-cell carcinoma of the bronchus. *J. Path. & Bact.*, 1959, **78**, 513–519.
5. Pearse, A. G. E. Histochemistry, Theoretical and Applied. Little, Brown & Co., Boston, 1953, p. 415.
6. Heaney, H. G. Extragenital chorionepithelioma in the male. *Am. J. Cancer*, 1933, **19**, 22–30.
7. Symeonidis, A. Über das Chorionepitheliom beim Mann und seine hormonale Wirkung in Form von "Schwangerschaftsveränderungen." *Beitr. path. Anat.*, 1934, **94**, 370–375.
8. Roth, F. Über die bösartigen Hodengewächse, insbesondere das Chorionepitheliom und die Möglichkeit der Spontanheilung des primären Hodenteratoids, mit einem Beitrag zur Frage des Diabetes insipidus. *Ztschr. Krebsforsch.*, 1950, **57**, 21–69.
9. Michel, G. Zur Frage der sogenannten extragenitalen Chorionepitheliome. *Frankfurt. Ztschr. Path.*, 1947, **59**, 59–68.
10. Eck, H. Über Spontanheilung bösartiger Geschwülste, besonders des malignen Hodenteratoms. *Zentralbl. Chir.*, 1952, **77**, 2240–2248.
11. Friedman, N. B. The comparative morphogenesis of extragenital and gonadal teratoid tumors. *Cancer*, 1951, **4**, 265–276.
12. Rather, L. J.; Gardiner, W. R., and Frerichs, J. B. Regression and maturation of primary testicular tumors with progressive growth of metastases; report of 6 new cases and review of literature. *Stanford M. Bull.*, 1954, **12**, 12–25.
13. Maluf, N. S. R.; Loeffler, R. K., and Erickson, E. E. Effect of bilateral adrenalectomy on metastatic choriocarcinoma from teratoma of the testis. *J. Clin. Endocrinol.*, 1956, **16**, 1217–1226.
14. Maring, H.; Knopp, J., and Langecker, H. Chorionepitheliom beim Manne. *Acta endocrinol.*, 1956, **21**, 289–298.
15. Craver, L. F., and Stewart, F. W. An unusual case of teratoma testis. *J.A.M.A.*, 1936, **106**, 1802–1804.

16. SYMEONIDIS, A. Betrachtungen über das Hodenteratoid, seine Metastasierung und das sog. "extragenitale" Chorionepitheliom an Hand eines narbigen stecknadelkopfgrossen rudimentären Hodenteratoids mit dreikeimblätterigen und Chorionepitheliommetastasen. *Virchows Arch. path. Anat.*, 1943, **311**, 509–518.

17. ROTTINO, A., and DEBELLIS, H. Extragenital chorioma: its relation to teratoid vestiges in the testicles *Arch. Path.*, 1944, **37**, 78–80.

18. RIOPELLE, J. L. Le chorio-épithéliome extragénital et ses relations avec un tératome latent du testicule. *Union Med. Canada*, 1948, **77**, 1399–1407.

19. MAGOVERN, G. J., and BLADES, B. Primary extragenital chorioepithelioma in the male mediastinum. *J. Thoracic Surg.*, 1958, **35**, 378–383.

20. GUICHARD, A., and CABANNE, F. Contribution à l'étude des chorio-épithéliomes pulmonaires chez l'homme et de leurs formes dites primitives. *J. méd. Lyon*, 1953, **34**, 235–265.

21. LYNCH, M. J. G. and BLEWETT, G. L. Choriocarcinoma arising in the male mediastinum. *Thorax*, 1953, **8**, 157–161.

22. STOWELL, R. E.; SACHS, E., and RUSSELL, W. O. Primary intracranial chorionepithelioma with metastases to the lungs. *Am. J. Path.*, 1945, **21**, 787–801.

23. BONN, H. K., and EVANS, N. Extragenital chorioepithelioma in the male with associated gynecomastia; report of a case. *Am. J. Surg.*, 1942, **58**, 125–132.

24. CHERNOFF, H. M.; EVANS, T. S.; BARTLETT, C. J., and SWIRSKY, M. Y. Extragenital chorionepithelioma in the male. *Arch. Int. Med.*, 1945, **76**, 347–351.

25. KRIVAK-KNEŽEVIĆ, Š. Ein Fall von extragenitalem Chorionepitheliom bei einem Manne. *Med. Klin. Berl.*, 1958, **53**, 1369–1371.

26. PORTMAN, J. Über das ektopische Chorionepitheliom beim Mann. *Beitr. path. Anat.*, 1959, **120**, 474–482.

27. SCHÄFER, H. Extragenitales Chorionepitheliom bei einem Mann. *Strahlentherapie*, 1959, **108**, 283–287.

28. WILLIS, R. A. Pathology of Tumours. C. V. Mosby Co., St. Louis; Butterworth & Co., London, 1953, ed. 2, p. 560.

29. WILLIS, R. A. The Borderland of Embryology and Pathology. Butterworth & Co., London, 1958, p. 450.

30. THEISS, E. A.; ASHLEY, D. J. B., and MOSTOFI, F. K. Nuclear sex of testicular tumors and some related ovarian and extragonadal neoplasms. *Cancer*, 1960, **13**, 323–327.

[*Illustrations follow*]

Legends for Figures

All photographs were prepared from sections stained with hematoxylin and eosin.

Fig. 1. (AFIP Acc. 589674, Neg. 59–3809) A hyalinized scar adjacent to the rete testis contains hematoxylin-staining bodies and a cluster of small cysts. × 20.

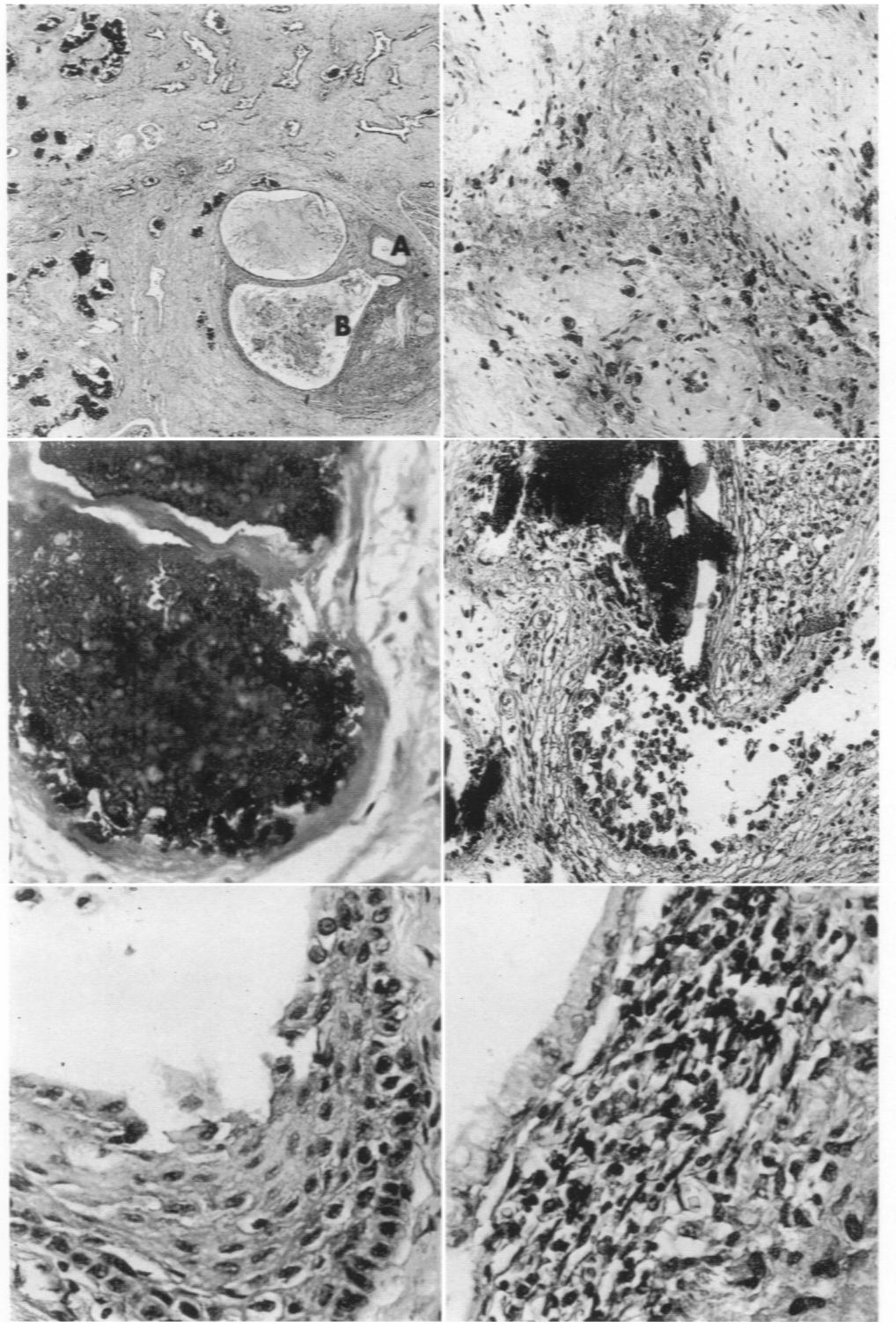
Fig. 2. (AFIP Acc. 168079, Neg. 60–113) A scar contains numerous siderophages. Note the fibrosed remnant of seminiferous tubules. × 130.

Fig. 3. (AFIP Acc. 323501, Neg. 59–6417) Amorphous granular, nonlaminated hematoxylin-staining material appears in the tubules. Note the hyalinized basement membrane and the complete absence of red or white cells. × 350.

Fig. 4. (AFIP Acc. 589674, Neg. 59–3806) Tubules contain both fragmented hematoxylin bodies and neoplastic cells. The cells resemble an undifferentiated embryonic type of carcinoma. × 165.

Fig. 5. (AFIP Acc. 589674, Neg. 59–6415) Higher magnification of area "A" in Figure 1, showing a cyst lined by squamous cells. × 440.

Fig. 6. (AFIP Acc. 589674, Neg. 59–6414) Higher magnification of area "B" in Figure 1, showing a cyst lined by tall columnar mucous epithelium. × 440.



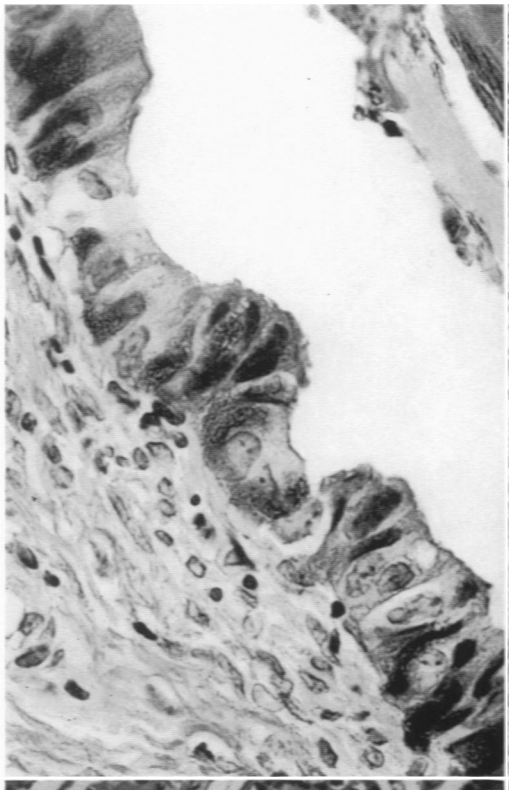
1 2 3 4 5 6

FIG. 7. (AFIP Acc. 927471, Neg. 59–5982) A mucous cyst from another case, showing enterochromaffin cells wedged between the bases of the columnar cells. × 530.

FIG. 8. (AFIP Acc. 589674, Neg. 59–5977) A small focus of typical seminoma from an area adjacent to a testicular scar. The cells are vacuolated and appear mostly in small groups. × 165.

FIG. 9. (AFIP Acc. 323501, Neg. 59–6419) Altered, hyperchromatic germ cells in the tubules surrounding a scar. × 130.

FIG. 10. (AFIP Acc. 323501, Neg. 59–6418) Higher magnification of Figure 9, showing hyperchromatic cells and vacuolation of the cytoplasm. Note the arrangement of Sertoli cells between the hyperchromatic abnormal germ cells and the lumen of the tubules. × 660.



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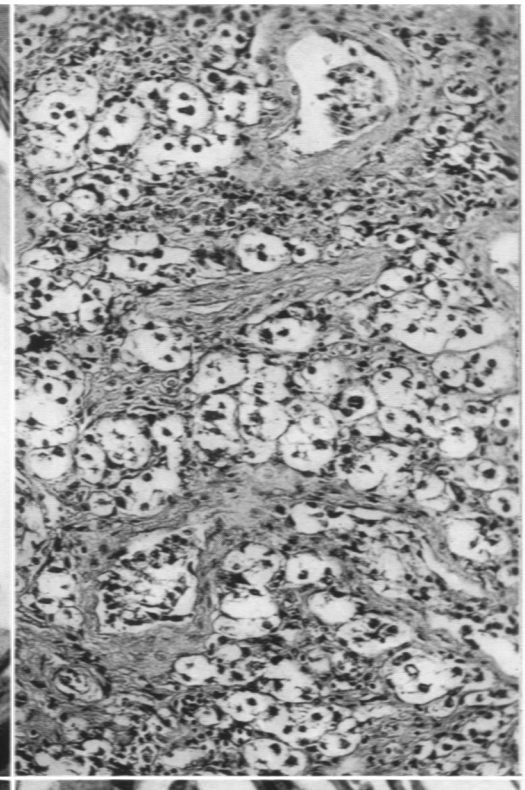

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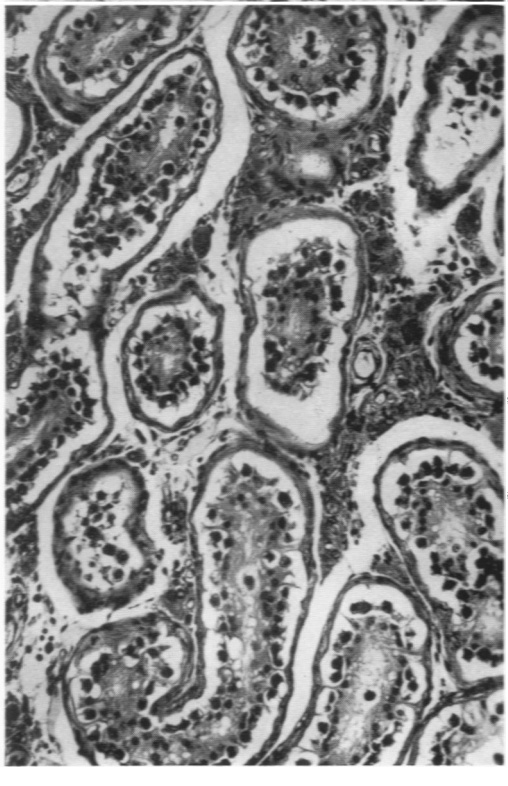

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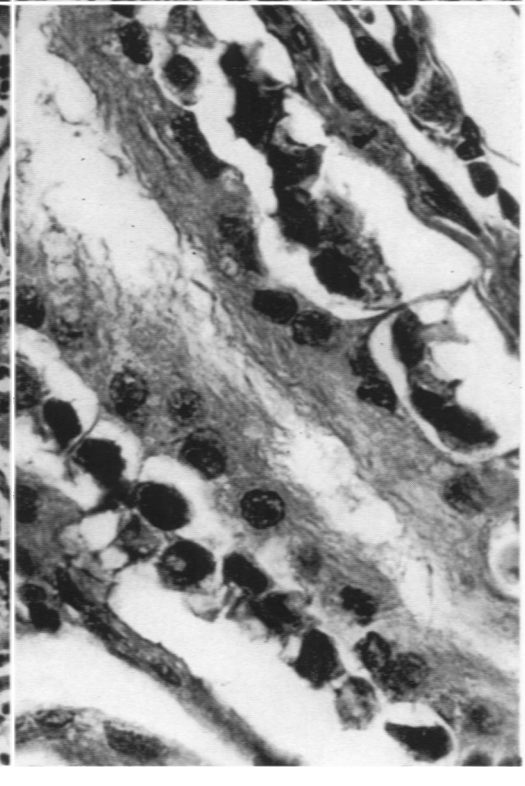

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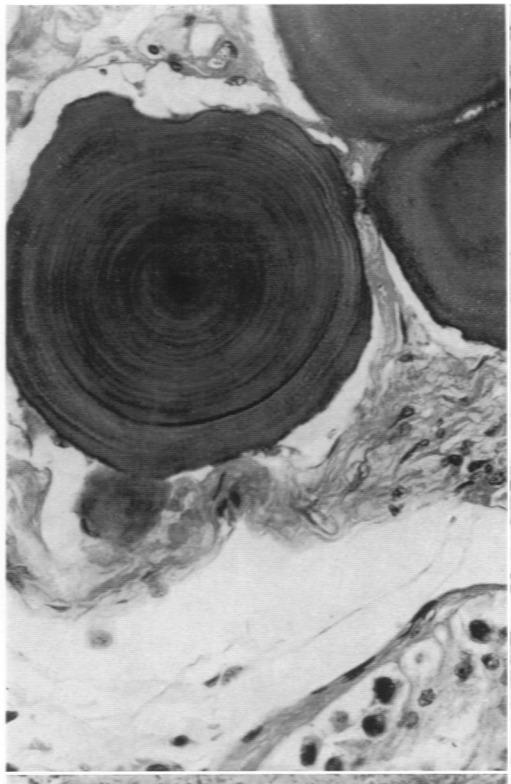
FIG. 11. (AFIP Acc. 323501. Neg. 59–5623) The structure of the mucospherules frequently observed in testes is shown. Note the concentric laminated appearance. × 305.

FIG. 12. (AFIP Acc. 307805. Neg. 59–3985) A solitary mucospherule frequently seen among persistent Sertoli cells in an undescended testis. × 195.

FIG. 13. (AFIP Acc. 480273. Neg. 59–4402) A teratoma of the testis, consisting chiefly of ossifying cartilage and adipose marrow. Note the hematoxylin-staining deposits in the adjacent scarred area. × 50.

FIG. 14. (AFIP Acc. 532644. Neg. 59–6422) A control case with grossly detectable embryonal carcinoma. In one area a typical hematoxylin-staining deposit is observed in intimate relationship to the neoplasm. This is believed to represent an area of necrosis in the tumor. × 42.



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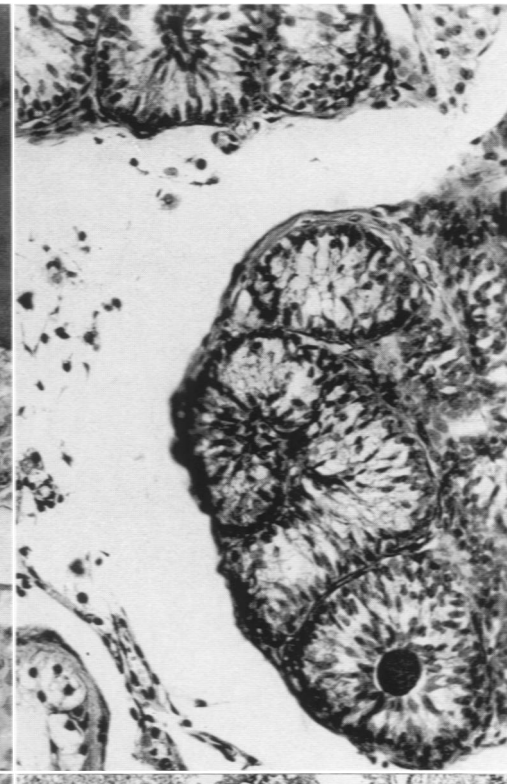

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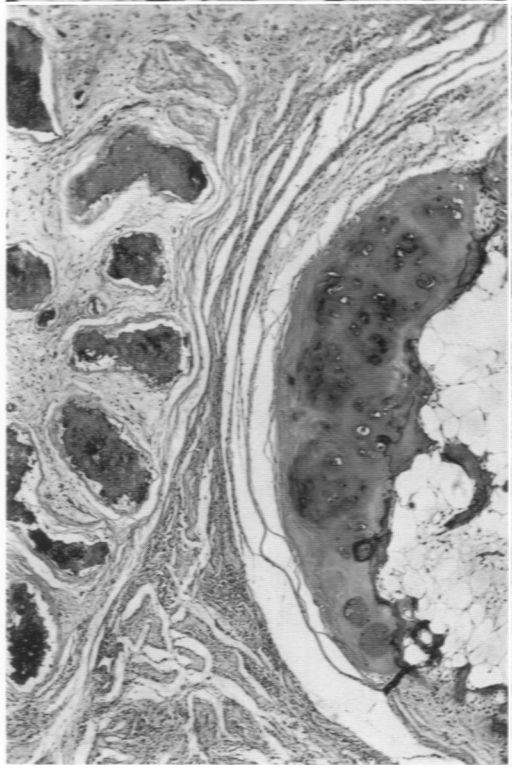

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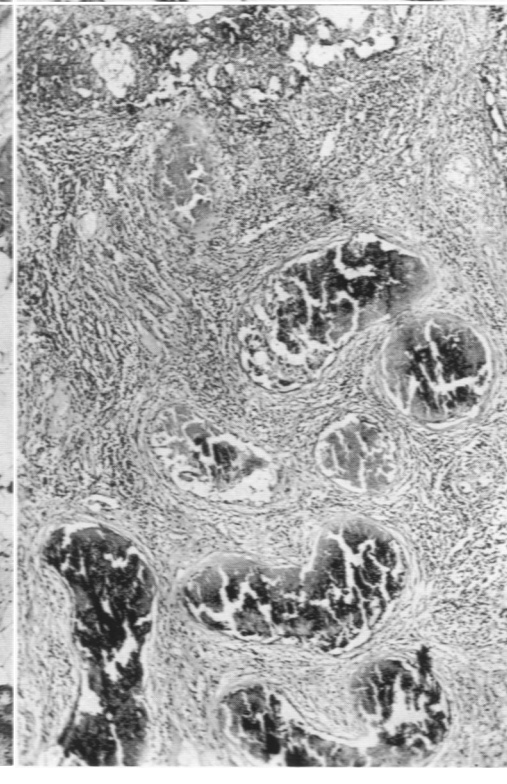

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